subjects. We plan to examine the biophysical defects by studying *in vitro* filament forming ability of the mutant myosin to determine if defective filament formation or instability of the myosin filaments is the basis of MSM. Our study will be an important step in exploring the mechanistic basis of MSM, and identify potential therapeutic approaches by over-expressing myosin chaperones or the autophagic response.

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Modulating HIV Infection by Controlling the Kinetics of SEVI Fibrillization

Kevin Hartman[1], Sharonne Temple[2], Nataliya Popovych[1], Kazuaki Monde[1], Jeffrey Brender[1], Akira Ono[1], Ayyalusamy Ramamoorthy[1].
[1]University of Michigan, Ann Arbor, MI, USA, [2]University of Deleware, Newark, DE, USA.

Despite the rapid progress of the AIDS pandemic, HIV is a surprisingly weak pathogen in vitro. The large difference between in vitro and in vivo infection rates suggests that cofactors absent in vitro but essential for the natural transmission of the virus may be responsible for this discrepancy. A recently identified peptide in human semen, $PAP_{248-286}$, has emerged as a candidate for the missing cofactor as it dramatically enhances the infectivity of HIV by up to five orders of magnitude. The $PAP_{248-286}$ peptide fragment has been shown to only induce its synergistic effect with HIV infection when in the form of amyloid fibers. Amyloid formation by $PAP_{248-286}$ into the active SEVI form is a slow process during which it is susceptible to being degraded and inactivated. Therefore, initiators of this fibrillization process would be an indirect cause of the increase in viral infectivity. For this reason, we have searched for possible inhibitors and enhancers of SEVI amyloid formation including metals, lipids, other amyloids, and polyphenolic inhibitors. The effects of the metals are metal specific, with some enhancing kinetics, while others either inhibit or have little effect. High resolution structures of $PAP_{248-286}$ and the green tea extract compound epigallocatechin gallate (EGCG) show binding to the monomer subunit through the lysine side-chains and inhibiting fiber growth, which could prove as an effective preventative measure for HIV infection. In contrast, amyloidogenic fibers produced by *E. coli* are seen to strongly enhance the kinetics of SEVI formation and HIV infectivity, indicating that bacterial infection could enhance the probability of HIV transmission. This phenomenon appears to be quite general and could be an important seeding mechanism for other amyloid proteins.

1) Biophysical. Journal (2009), 97(9), 2474-2483.
2) Biochemica et Biophysica Acta, Biomembranes (2011), 1808(4), 1161-1169.

1285-Pos Board B55

A Statistical Mechanical Approach to Protein Aggregation

John Schreck, Jian-Min Yuan.
Drexel University, Philadelphia, PA, USA.

We develop a theory of aggregation using statistical mechanical methods. An example of a complicated aggregation system with several levels of structures is peptide/protein self-assembly. The problem of protein aggregation is important for the understanding and treatment of neurodegenerative diseases and also for the development of bio-macromolecules as new materials. We write the effective Hamiltonian in terms of interaction energies between protein monomers, protein and solvent, as well as between protein filaments. The grand partition function can be expressed in terms of a Zimm-Bragg-like transfer matrix, which is calculated exactly and all thermodynamic properties can be obtained. We start with a two-state treatment that can be easily generalized to three or more states using a Potts model, for which the exactly solvable feature of the model remains. We focus on $n \times N$ ladder systems, corresponding to the ordered structures observed in some real fibrils. We have obtained results on nucleation processes and phase diagrams, in which a protein property such as the aggregate concentration is expressed as a function of the initial protein concentration and inter-protein or interfacial interaction energies. We have applied our methods to Aβ(1-40) and Curli fibrils and obtained results in good agreement with experiments.

1286-Pos Board B56

Fusion Proteins are Able to Form Amyloid Structure

Vitaly A. Balobanov[1], Anna G. Egorova[1], Rita V. Chertkova[2], Nelly B. Ilyina[1], Victor D. Vasilyev[1], **Valentina E. Bychkova**[1].
[1]Institute of Protein Research, Russian Academy of Sciences, Pushchino, Moscow Region, Russian Federation, [2]Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russian Federation.

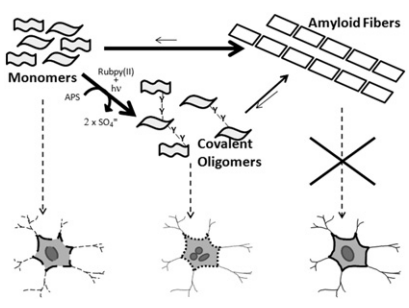
As shown previously, practically every protein can form amyloid structures in appropriate conditions. It is of great interest to investigate fusion proteins because they are used to produce target proteins. This study is focused on amyloid formation by fusion proteins with thioredoxin and artificial proteins. Aggregation of fusion thioredoxin-albebetin proteins was investigated by overnight incubation at 37°C. This process was monitored by light scattering, fluorescence, and electrophoresis. Properties of the aggregates were determined by far UV CD, electron microscopy, and X-rays diffraction. Trp fluorescence was used to observe changes specifically in thioredoxin. Kinetics of aggregate formation and urea equilibrium unfolding were monitored by Trp fluorescence. Amyloid-like properties of the fusion proteins were revealed using thioflavin T binding and X-rays diffraction. The latter gave 4.5 and 11 Å reflexes typical of the cross-beta structure. Unchanged Trp fluorescence indicated that thioredoxin retained its structure and was not involved in amyloid formation. This fact was also confirmed by urea unfolding. The mode of Trp fluorescence changes was evidence for unchanged thioredoxin properties before and after incubation of fusion proteins at 37°C, as well as in its free state. This means that amyloids were formed by albebetin alone. It should be stressed that unbound albebetin mutants form amyloid structures at 45°C, but when in fusion proteins, the event occurs as early as at 37°C. Such a behavior suggests that in fusion proteins the albebetin structure was destabilized, which might facilitate the amyloid formation. Destabilization of a target protein structure might influence its yield.This work was supported in part by RFBR 09-04-01348, RAS MCB Program.

1287-Pos Board B57

Oxidative Modification of Alpha-Synuclein Modifies its Cytotoxicity

Lisandro J. Falomir-Lockhart[1], Claudio D. Borsarelli[2], Veronika Ostatnà[3], Jonathan A. Fauerbach[4], Emil Palècek[3], Elizabeth A. Jares-Erijman[4], Thomas M. Jovin[1].
[1]Max Planck Institute for Biophysical Chemsitry, Göttingen, Germany, [2]Laboratorio de Cinética y Fotoquímica. INQUINOA - Universidad Nacional de Santiago del Estero, Santiago del Estero, Argentina, [3]Institute of Biophysics, Academy of Sciences of the Czech Republic, Brno, Czech Republic, [4]Departamento de Química Orgánica, Universidad de Buenos Aires, Buenos Aires, Argentina.

Parkinson's disease is a progressive neurodegenerative disorder, histologically defined by intracellular aggregates of proteins and lipids, associated with selective loss of dopaminergic neurons. The protein alpha-Synuclein (aSyn) is the most abundant component in these aggregates and has been identified as a key player in a series of neurodegenerative diseases. Early intermediates are thought to be the main ''culprits'', in combination with oxidative stress and lipid oxidation. Nevertheless, a comprehensive description of the relationship between protein aggregation and selective neuronal death is still missing. Photo-tunable oxidative modifications of aSyn were achieved using a sensitizer-dependent radical mechanism to generate stable covalent oligomers by specific crosslinking of Tyr residues. Different species were isolated and characterized by a complementary set of techniques, such as spectroscopy, electrochemistry and biochemical characterization that demonstrated the presence of diTyrosine crosslinkings. This led to reduced aggregation *in vitro*, possibly stabilizing more toxic species or avoiding its neutralization into amyloid fibers. Furthermore, modified covalent oligomer showed increased toxicity upon exposure of differentiated SH-SY5Y cells.



These results indicate that oxidative modifications seem to alter the conformation of aSyn and its tendency to aggregate, presumably impairing aSyn functions and promoting the development of its neuropathologies.

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Role of (htt^{NT}) α-Helix Formation in Huntingtin N-Terminal Fragment Aggregation

Rakesh Mishra, Ravindra Kodali, Bartholomew Roland, Ronald B. Wetzel.
University of Pittsburgh, Pittsburgh, PA, USA.

The N-terminal 17 amino acid sequence in huntingtin (htt^{NT}) plays a crucial role in the aggregation of htt N-terminal fragment peptides (htt NTFs). In the current mechanistic model, htt^{NT} segments pack into α-helical bundles to form oligomers that create high local concentrations of appended polyglutamine (polyQ) segments, favoring nucleation of polyQ amyloid. Consistent